

Claims

I claim:

1. A substantially monodisperse polyglutamate polymer comprising a
5 polyglutamate polymer having a polydispersity (M_w/M_n) of less than about 1.3.

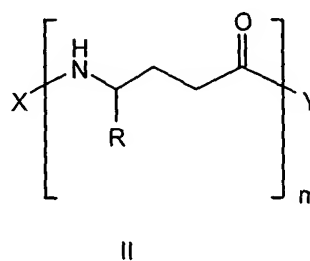
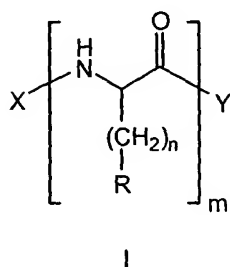
2. The monodisperse polyglutamate of claim 1, wherein the polydispersity
(M_w/M_n) is less than about 1.2.

10 3. The monodisperse polyglutamate of claim 1, wherein the polydispersity
(M_w/M_n) is about 1.1 or less.

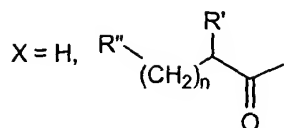
4. A method of inhibiting nitric oxide synthase III (NOS III) in a mammal, which
comprises administering to said mammal one or more polyglutamate polymers having a
15 molecular weight of at least 100,000 Daltons in an amount effective to inhibit the activity
of NOS III in said mammal.

5. The method of claim 4 wherein the polyglutamate polymer comprises one or
more polymers of the formula I (α -polyglutamate) or formula II (γ -polyglutamate)

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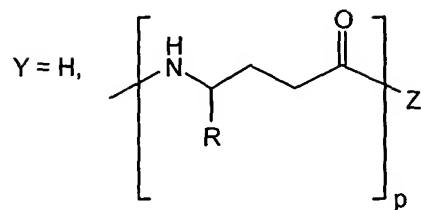


wherein



$$Y = H, \left[\begin{array}{c} \text{H} \\ | \\ \text{---} \text{NH} \text{---} \text{CH} \text{---} \text{C}(=\text{O}) \text{---} \\ | \quad \quad | \\ (\text{CH}_2)_n \quad \text{Z} \\ | \\ \text{R} \end{array} \right]_p$$

and for formula II:

[illegible]

wherein $m = 1-70,000$; $n = 1-5$, $p = 0-3$, $q = 1-6$, $r = 1-6$ and R may also represent the metal salts of carboxylic acids when $R = \text{COOH}$ where the metal is an essential metal selected from the group consisting of aluminum, calcium, iron, lithium, manganese, magnesium, copper, selenium, and zirconium.

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6. The method of claim 5, wherein the γ -polyglutamate is monodisperse and has a poly dispersity of less than about 1.3.

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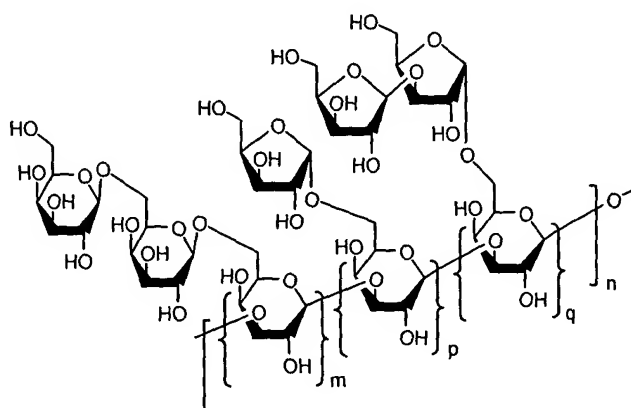
7. The method of claim 5, wherein the γ -polyglutamate has a molecular weight of about 1,000,000 Daltons.

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8. A method of inhibiting nitric oxide synthase III (NOS III) in a mammal, which comprises administering to said mammal one or more arabinogalactan compounds having a 1,3- β -D-galactan backbone with 1,6- β -D-galactobiose, 1,3- β -L-arabinofuranosyl- α -L-arabinofuranose, and α -L-arabinofuranose branch units and a molecular weights of from about 6,000 to about 2,500,000 Daltons in an amount effective to inhibit the activity of NOS III in said mammal.

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9. The method of claim 8, wherein the arabinogalactan is a compound of the formula III:



III

5 10. The method of claim 9, wherein m is between 100 and 200; q is between 20-30; p is 3, 4 or 5 and n is about 90.

15 12. The method of claim 11, wherein the molecular weight of the acacia compounds is about 250,000 Daltons and the compound contains L-rhamnose branches.

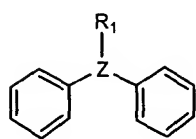
$$\text{Y-(X)}_m\text{-R} \quad \text{(IV)}$$

Y represents H, $(\text{CH}_2)_n$, $\text{O}(\text{CH}_2)_n$, $[(\text{CH}_2)_2\text{O}]_n$, $\text{N}(\text{CH}_2)_n$, alkyl, amino acid, or carbohydrate, (trishydroxymethyl)aminomethane and where $n = 1-6$;

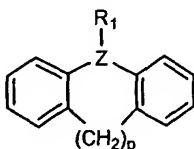
R represents H, alkyl, amino acid, carbohydrate, halogen, (trishydroxymethyl)aminomethane, polyol or acyl residue; and

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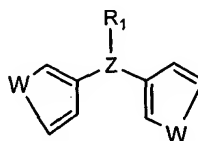
phenyl, piperidine, pyridine, pyrrolidone, pyrrole, triazine, triphenylmethane, tryptamine, alkyl-, aryl, and halogen-substituted derivatives thereof, or a substituent of one of the formulas V-XI:



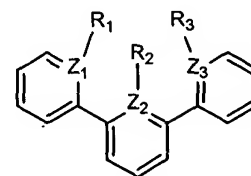
V



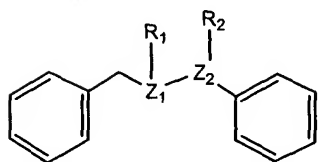
VI



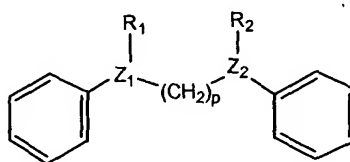
VII



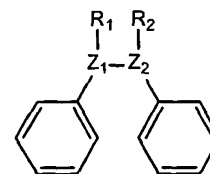
VIII



IX



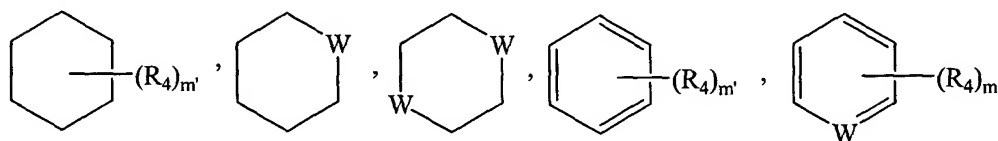
X



XI

wherein Z, Z₁, Z₂, Z₃ represents (CH₂)_p, C=O, CHO, N, NH, C=CHR₁, CH-NH, C=NNH, O, or S;

R₁, R₂, R₃ represent (CH₂)_kR₄, O(CH₂)_kR₄, OH, carbohydrate, an amino acid, (trishydroxymethyl)aminomethane,



R₄ represents H, alkyl, halogen, N-alkyl, (trishydroxymethyl)aminomethane

W = CH₂, CH₂R₅, CH, CHR₅, N(R₅)_j, N, O, S, C=O

R₅ = H, F, OH, alkyl, aryl and

where j = 1-2, k = 1-6, m' = 1-5, p = 1-10, q = 1-6.

14. A method of inhibiting nitric oxide synthase III (NOS III) in a mammal, which comprises administering to said mammal one or more polymeric metal complexes of Formula XII



(XII)

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wherein P is an anionic polymer, selected from the group consisting of a polysaccharide, oligosaccharide, or a polypeptide polymer; and M is a neuroprotective metal ion selected from the group consisting of aluminum, calcium, copper, lithium, magnesium, manganese, selenium, iron and zirconium and pharmaceutically acceptable salts thereof in an amount effective to inhibit the activity of NOS III in said mammal.

15. The method of claim 14, wherein the polymeric metal complex is a polysaccharide iron complex or a poly(glutamic acid) iron complex.

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16. A method of inhibiting nitric oxide synthase III (NOS III) in a mammal, which comprises administering to said mammal an effective NOS III inhibiting amount of one or more tripeptides selected from the group consisting of arginine-glutamate-arginine, arginine-asparagine-arginine, lysine-glutamate-arginine, arginine-glutamate-lysine, ornithine-glutamate-arginine, arginine-glutamate-ornithine, citrulline-glutamate-arginine, arginine-glutamate-citrulline, N-acetyl-arginine-glutamate-arginine, arginine-glutamate-arginine-NH₂, arginine-glutamate-arginine-OCH₃, D-arginine-L-glutamate-arginine, L-arginine-D-glutamate-arginine and L-arginine-L-glutamate-arginine.

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17. A method of inhibiting nitric oxide synthase III (NOS III) in a mammal, which comprises administering to said mammal an effective NOS III inhibiting amount of one or more compounds selected from the group consisting of *p*-Aminoclonidine; Aminopentamide; Amperozide; Atenolol; Atropine; Bepridil; Bietanautine 1,2,3,6-Tetrahydro-1,3-dimethyl-2,6-dioxo-7H-purine-7-acetic acid compound with 2-(diphenylmethoxy)-N,N-dimethylamine (2:1); 1-(2-(Bis-(4-fluorophenyl)methoxy)ethyl)-4-(3-phenylpropyl)-piperazine; 1-(2-(Bis-(4-fluorophenyl)methoxy)ethyl)-4-(3-phenyl-

2-propenyl)-piperazine); Bromocriptine; Buaverine; Bulan; Buspirone HCl; Butyl-N-ethyl-2-(1-naphthyloxy); Clonidine; Ephedrine; Ethaneamine; Calmidazolium chloride; Carbamazepine; Cetinzne; Cetrizine; Chicago Sky Blue 6B; 1-(2-Chlorobenzoyl)piperazine-2,3-dicarboxylic acid, Na; 2-Chloro-11-(4-methylpiperazino)-dibenzy[b,f]oxepin]; 3 α [(4-Chlorophenyl)phenylmethoxy]tropane; Cinnarizine; Ciprofloxacin; Clomipramine; Cyproheptadine; Deoprenilamine; Deofenine; Deprenyl; N-Desmethyldiazepam; Diazepam; (2-(3,4-Dichlorophenyl)-N-methyl-[(1S)-1-phenyl-2-(1-pyrrolidinonyl)ethyl](acetamide); (RS-[3-[1-[(3,4-Dichlorophenyl)acetyl]methylamino]-2-(1-pyrrolidinonyl)ethyl]phenoxy] acetic acid); N,N-Diethyl-2[4-phenylmethyl]phenoxy]ethanamine); 4,4'-Difluoro-3 α -(diphenylmethoxy)tropane hydrochloride; 1,1-Dimethyl-4-diphenylacetoxypiperinium iodide (4-DAMP); Dimepheptanol; Diphenhydramine HCl; Diphenidol; Diphenolic acid; (1-(4,4-Diphenyl-3-butenyl)-3-piperidinecarboxylic acid); [1-(2-Diphenylmethoxyethyl)-4-(3-phenylpropyl)-piperazine]; [1-(2-Diphenylmethoxyethyl)-4-(3-phenyl-2-propenyl)-piperazine]; Diphenylpyraline; Dipipaone; Doxepin; Doxylamine; Droloxifene; Edrophenoium chloride; Emeponium bromide; Ergonamine; Ergotamine; Etastine; Etifelmin; Etodioxazine; Ethylbenzhydramine; Ethylbentropine; Felodidine; Fendiline; Feniprane; Fenoprofen; Fempiverinium bromide; Fexofenadine; Fludpirilene; Flufenamic acid; Flunarizine; Fluoxetine; Flupentixol dihydrochloride; Fluphenazine-N-2-chloroethane; Flusipirilene; Galanthamine hydrobromide; Genistein; N-[3-(1-Hexahydroazapinyl)propyl]-a-cyclohexylbenzeneacetamide; Ifenprodil; Imipramine; Ipatropium bromide; Isomethadol; Isomethadone; Ketanserin tartrate ; Ketotifen fumerate; Levomethadyl acetate; Lidoflazine; Lorazepam; Lupinifolin; Lupinifolinol; Meperidine; Methadone; Methadyl acetate; Methiothepin maleate; 2-[2-(4-(2-Methoxyphenyl)piperazine-1-yl)ethyl]-4,4-dimethyl-1,3-(2H,4H)-isoquinolindione HCl; d-Methylphenidate ; Mianserin HCl ; Naftopidil dihydrochloride; Neostigmine; Noracymethadol; Normethadone; Norpipanone; Oxatomide; Oxazepam; Penfluridol; Pentacynium bis(methylsulfate); Pergolide; Phenadoxone; Phenoxybenzamine; Phentolamine; α -Phenyl-1-(2-phenethyl)-4-piperidinemethanol; Physostigmine; Pimozide; Piocarpine; Pirenzepine dihydrochloride; Propanolol; Pyridostigmine bromide; Rilmenidine; Rimcazole

dihydrochloride; Ritanserin; Robinetin; 12-epi-Scalaradial; Scopilamine; Selegilline; Sennoside; Sertraline; Sulpiride; Tacrine; Tamoxifen; Tamoxifen, 4-hydroxy/ 3-hydroxy; N,N,N',N'-Tetrakis-[(2-pyridylmethyl)ethylenediamine]; Thiothixene HCl; Trifluoroperazine; Trihexyphenidyl hydrochloride; 3-Tropanyl-3,5-dichlorobenzoate; Yohimbine; and Zimelidine dihydrochloride.

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